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EXAMINER	
ART UNIT	PAPER NUMBER
1804	7

18N2/1125

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DATE MAILED: 11/25/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 9/3/96 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-39 are pending in the application.
   Of the above, claims 3-5, 13-18, 23, 25-28, 33-34 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-2, 6-12, 19-22, 24, 29-32, 35-39 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

1. The amendment filed 9/3/96 (Paper No. 6) has been entered. Claims 1-36 remain and newly advanced claims 37-39 are pending in the instant application. It is noted that Applicants wish to cancel claims covering non-elected subject matter (see page 3, Paper No. 6, under "Remarks"). However, requests for claim cancellations must be made under the "In The Claims" section of an amendment. Therefore, all claims remain pending in the instant application.

2. Applicant's election of Group I, claims 1-2, 6-12, 19-22, 24, 29-32 and 35-36 in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)).

3. Claims 3-5, 13-18, 23, 25-28 and 33-34 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in Paper No. 6.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification stands objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure for the reasons of record advanced in the preceding office action, Paper No. 4, and as addressed below in the restatement of the grounds for rejection. Applicants' arguments filed 9/3/96 (Paper No. 6) have been fully considered but they are not deemed persuasive.

Applicants' arguments concerning the use of CREB promoters is deemed persuasive. However, the specification fails to provide an enabling disclosure for the use of a tetracycline responsive promoter. Sequences, or directions to obtain sequences, for these inducible promoters have not been provided in the specification. Even if the gene sequences for these promoters were known at the time of the invention, applicants have failed to supply evidence which would indicate that these promoters would function effectively in 293 cells.

It is maintained that the specification fails to provide an enbling disclosure for cell line which can complement an E1/E2a/E4-deleted adenovirus. Because the regulation of these proteins (E1, E2a and E4) must be tightly controlled, it is not clear that one could create such a cell line.

Newly advanced claims 38 and 39 lack written description in the specification. The specification fails to provide support for a replication-defective

recombinant adenovirus which contains a deletion in the E4 region, wherein ORF 4 is neither deleted or mutated. The specification also fails to provide support a packaging cell that supports the growth of a replication defective recombinant adenovirus that carries a deletion of the adenovirus rep gene region.

5. Claims 9, 24, 38 and 39 stand rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 11-12, 19-22 and 29-31 stand rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Engelhardt *et al.* [PNAS USA, 91:6196-6200 (1994)].

Engelhardt *et al.* disclose a replication-deficient adenoviral vector which contains deletions in the E1 and E3 regions, as well as a mutation at base 1064 in the E2A region (see page 6196, last paragraph). Engelhardt *et al.* teach the use of

293 cells for propagation of the disclosed vectors on page 6197, paragraph 2. Mouse liver cells were transfected with the adenoviral vectors containing a transgene (lacZ).

In response to Applicants' arguments, the Examiner does not contest the fact that the exemplified vectors and packaging cell lines in the instant application differ from those of Engelhardt *et al.*. However, Applicants' claims clearly encompass the vector (Ad.ts125CBlacZ), cell line (293 cells), and method for infecting mammalian target cells disclosed by Engelhardt *et al.*. Consequently, Applicants' claims stand rejected.

8. Claims 19-22 and 36-37 stand rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Armentano *et al.* [J. Cellular Biochemistry, 18:222 (1994)].

In response to Applicants' argument that Armentano *et al.* do not teach certain features of Applicants' invention, the limitations on which the Applicant relies (i.e., lethal delettions/mutations) are not stated in the claims. Therefore, it is irrelevant whether the reference includes those features or not.

9. Claims 1-2 and 11-12 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Klessig *et al.* [Molecular and Cellular Biology, 4(7):1354-1362 (1984)].

Klessig *et al.* disclose a DNA plasmid (pMSG-DBP) comprising an adenoviral gene (E2a) encoding a cytoxic protein (DBP) operably linked to an inducible promoter (the dexamethasone-inducible promoter of MMTV). Klessig *et al.* further disclose a 293 cell line which could complement E1/E2a-deleted adenoviruses on page 1361, first paragraph. Consequently, Applicants' claims are clearly anticipated.

10. Claims 11-12 and 35 are rejected under 35 U.S.C. § 102(b) as being anticipated by Graham *et al.* [J. General Virology, 36:59-74 (1977)].

Graham *et al.* describe the creation of 293 cells, which support the growth of adenoviruses containing deletions in the E1 and E4 regions (except ORF 6), as evidenced by the statement on page 12 of Paper No. 6, where Applicants' state that "wild type 293 cells may be used to package the Armentano virus." The "Armentano" virus to which Applicants are referring is the vector which contains deletions in the E1, E3 and E4 regions of the genome (see the 102(a) rejection of this office action). Consequently, 293 cells are encompassed by Applicants' claims.

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior

> art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

12. Claims 1-2, 6-12, 19-22, 24, 29-32, and 35-37 are rejected under 35 U.S.C. § 103 as being unpatentable over Weinberg *et al.* [PNAS USA, 80:5383-5386 (1983)], Gregory *et al.* [WO 94/12649], Su *et al.* [Biochemical and Biophysical Research Communications, 186(1):293-300 (1992)], and Pei *et al.* [Mol. Enocrinol., 5(4):521-534 (1991)].

In response to Applicants' arguments, it is the Examiner's assertion that the combination of the above references not only suggests the claimed invention as described in the previous office action, Paper No. 4, but also provides a reasonable expectation of success. Applicants argue that "the art simply does not provide the suggestion of deleting both E1 and E4." This is not the case, however, as evidence by the quotation cited in the previous office action which stated:

> A cell line could in theory be established that would **fully** complement E4 functions deleted from a recombinant virus. The problem with this approach is that E4 functions in the regulation of host cell protein synthesis and is therefore toxic to cells. The present recombinant adenoviruses are deleted for the E1 region and must be grown in 293 cells which complement

> E1 functions. The E4 promoter is activated by the E1a gene product, and therefore to prevent inadvertent toxic expression of E4 transcription of E4 must be tightly regulated. The requirements of such a promoter or transactivating system is that in the uninduced state expression must be low enough to avoid toxicity to the host cell, but in the induced state must be sufficiently activated to make enough E4 gene product to complement the E4 deleted virus during virus production. (emphasis added)

In response to Applicants' piecemeal analysis of the references, one cannot show non-obviousness by attacking references individually where, as here, the rejections are based on combinations of references.

In response to Applicants' argument that there is no suggestion to combine the references, the Examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CCPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA) 1969. In this case, Gregory *et al.* clearly teach that an inducible promoter should be used to control expression of the E4 gene. Because the promoter

described by Su *et al.* and Pei *et al.* was such an inducible promoter, one of skill in the art would have been motivated to use it.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. Curtis Hogue, Jr. whose telephone number is (703) 308-1083. The examiner can normally be reached on Monday-Friday from 7:30 a.m. to 4:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jackie Stone, can be reached on (703) 308-3153. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JACQUELINE M. STONE
SUPERVISORY PATENT EXAMINER
GROUP 1800

D. Curtis Hogue, Jr.

November 19, 1996